

Uric acid, blood pressure, and gout management

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VALORISATION

An important aspect of research is to ensure its results will have, besides scientific merit, also social and economic value. This addendum describes how society may benefit from the work conducted in this thesis.

Gout is the most prevalent form of inflammatory rheumatic disease and affects 1 – 2% of the population worldwide.¹ The prevalence is particularly high among men, and approximately 7% of men above 65 are affected.² Hyperuricemia, the most important risk factor for gout, is with a prevalence of 20% far more prevalent than gout. Recent studies showed that both gout and asymptomatic hyperuricemia have been associated with an increased risk for cardiovascular disease, cardiovascular mortality and all-cause mortality.³⁻⁵ Moreover, patients with gout or asymptomatic hyperuricemia have higher all-cause health care utilization and cost compared with those without a diagnosis of gout or without hyperuricemia.⁶⁻⁸ For example, the estimated all-cause total direct costs was \$16,925 per elderly gout patient and \$10,590 for a non-gout patient.⁹ Overall, gout and asymptomatic hyperuricemia impose a significant economic and social burden for society.¹⁰

While elevated serum uric acid is a clear risk marker for gout, the role of uric acid in the development of high blood pressure (hypertension) and cardiovascular disease remains uncertain. Since there is biological evidence that the production of uric acid might lead to vascular dysfunction and elevated blood pressure it is of interest to investigate this hypothesis.^{11,12} In *Part I* of this thesis we therefore investigated the role of uric acid production, as an underlying mechanism, in the association between uric acid and blood pressure. Our findings suggest that overproduction of uric acid might be involved in the pathogenesis of hypertension. Although the study outcomes from *Part I* of this thesis may not directly lead to societal benefit at first, they can increase insight into the association of uric acid with hypertension and cardiovascular disease and may lead to further research initiatives.

Overall the studied proxies need to be validated in biological experiments to establish if they reflect increased uric acid production. Furthermore, the present findings need to be confirmed in other existing datasets. If confirmed, defining the threshold for uric acid overproducers at risk for developing hypertension is required. Finally, randomized controlled trials are needed to examine whether in uric acid overproducers inhibitors of uric acid production reduce (high) blood pressure or prevent the development of hypertension.

If our hypothesis will be confirmed, the identification of uric acid overproducers might be valuable to identify people who are at high risk for developing hypertension and cardiovascular disease. Today only 37% of the hypertensive patients obtain a well-

controlled blood pressure.¹³ Even this estimate is conservative; the average expenditure for a hypertensive patient in the United States is about \$1320 per year.¹⁴ In other words, uncontrolled blood pressure is a high health burden for the patient and economic burden for society. Therefore, a better understanding of the underlying pathophysiology, the identification of persons at risk and novel pharmacological treatment is of main importance.

In the management of chronic gout, a substantial group of patients need long-term management with uric acid lowering therapy. From the findings of *Part II* of this thesis it appears that poor medication adherence among gout patients is common. We found that less than 40% of the patients in whom allopurinol treatment is started are adherent to their medication. Moreover, although patients who have stopped therapy are likely to return, the chances of a backlash are as likely.

Assuming that uric acid lowering therapy is initiated for the right reasons, non-adherence may not only lead to a higher health-burden for the patient, but may also lead to an economic burden due to additional health care expenditures in those with more advanced and possibly complicated gout. In order to improve medication adherence insights into factors associated with poor medication adherence should be known. The results of this thesis gave a good overview of demographic as well as clinical patient characteristics which were associated with poor medication adherence. Health care providers should provide extra support to those patients who are at high risk for poor medication adherence. Target groups are younger and 'healthier' patients, including patients with a normal weight, who are not on antihypertensive medication, and do not suffer from comorbidities like diabetes or hypertension. Although we identified patients at high risk, the exact rationale for interrupting or stopping medication usage was seldom studied. More insight into patients' understanding of the disease and medication and involved concerns is needed.

As gout is mainly treated in primary care and as poor medication adherence can be either a patient behaviour or provider directed, we explored the knowledge, illness perceptions and stated clinical practice behaviour of general practitioners when managing gout. The attitude about adherence was surprising since almost all general practitioners prefer to wait for recurrent attacks instead of actively screening for adherence. Moreover, if the problem of non-adherence is not addressed, they might draw the false conclusion that the medication is not effective and change to other, often more expensive, medications. Therefore, general practitioners should be more aware of the problem of non-adherence and take responsibility therein.

Changing clinical practice behaviour is a challenge, next to an educational program for general practitioners on the problem and importance of medication adherence, it is of utmost importance to elucidate the general practitioners' opinion on the long-term

management of gout. Moreover, as discussed in the *Discussion* section of this thesis, further research should focus more on patients seen in primary care instead of those patients seen in secondary care. Eventually, this teaches us what the best strategy and target is for the long-term management of gout and would provide evidence-based recommendations for the treatment of gout in primary care.

Since non-adherence has consequences for the patient's health, health care provider, and society, medication adherence should be seen as a shared responsibility. It is a reasonable, although not yet proven assumption, that successful long-term management should improve individual's health and reduce the financial burden of gout. Thus far, little is known on the consequences of poor medication adherence, we therefore recommend further studies to investigate the impact of poor medication adherence on the patient's health, quality of life, health care utilization and related costs for society. These data can be the starting point for cost-effectiveness studies into adherence improvement programs.

In the end, the results of this thesis contribute to a better understanding of the role of uric acid in the development of hypertension. However, only after confirmation and when causality is established the societal utilization of the present findings may be feasible. Even if this only accounts for a small proportion of the total risk for hypertension and cardiovascular disease, addressing this may lead to a personalized approach and thereby a better public health. In addition, the results presented in this thesis emphasize the need for more awareness among health care providers for medication adherence. Whereas rheumatologists play an important role in treating the more severe cases of gout, general practitioners are the key player for most gout patients. This should be translated into intervention programs for improving medication adherence in a representative, thus mainly patients treated in primary care, gout population.

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